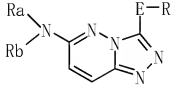
**AMENDMENTS TO THE CLAIMS**

**This listing of claims will replace all prior versions and listings of claims in the application:**

**LISTING OF CLAIMS:**

1. (withdrawn) A pharmaceutical composition which is a bone mass increasing inducer, comprising a non-living body-derived non-peptide osteoblast differentiation promoting compound as the first component and a bisphosphonate as the second component.

2. (withdrawn) The pharmaceutical composition described in claim 1, wherein the first component is a nitrogen-containing heterocyclic compound represented by the following general formula (I) or a salt thereof



(I)

(symbols in the formula have the following meanings,

Ra and Rb: the same or different and each represent H; CO-lower alkyl; $SO_2$-lower alkyl; an optionally substituted cycloalkyl; an optionally substituted aryl; or a lower alkyl which may have 1 to 3 substituents selected from the group consisting of an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted 4- to 8-membered monocyclic

saturated or partially unsaturated heterocyclic ring, CO-lower alkyl, $SO_2$-lower alkyl, $OR^1$, $SR^1$, $NR^1R^2$, a halogen, $NO_2$, CN and $COOR^1$; provided that at least one of Ra and Rb represents a group other than H; or,

Ra and Rb taken together with an adjacent N atom form a 4- to 8-membered saturated or partially unsaturated heterocyclic ring containing 1 or 2 N atoms as heteroatoms, said heterocyclic ring may be fused with a benzene ring or a cycloalkyl ring and may have a bridge and may form a spiro ring, and said heterocyclic ring may have from 1 to 5 substituent groups,

E: a single bond, a $C_{1-3}$ alkylene, vinylene (-C=C-), ethynylene (-C≡C-), CO, $NR^3$, $CH_2$-J, $CONR^4$ or $NR^5CO$,

J: O, S, $NR^6$, CO, SO or $SO_2$,

R: an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl or an optionally substituted 4- to 8-membered monocyclic saturated or partially saturated heterocyclic ring,

$R^1$ to $R^6$: the same or different and each denotes H or a lower alkyl;

with the proviso that the following compounds are excluded:

(1) a compound wherein Ra and Rb taken together with an adjacent N atom form a piperidino, E is a single bond and R is a piperidino, unsubstituted phenyl, *p*-(trifluoromethyl)phenyl, *p*-chlorophenyl or *o*-nitrophenyl,

(2) a compound wherein Ra and Rb taken together with an adjacent N atom form a 4-methyl-1-piperazinyl, E is a single bond, and R is an unsubstituted phenyl, *p*-methylphenyl, *m*-methylphenyl, *p*-methoxyphenyl, *m*-chlorophenyl, *p*-chlorophenyl or *m*-nitrophenyl,

(3) a compound wherein R is an optionally substituted imidazolyl, 5-nitro-2-furyl or 5-nitro-2-thienyl,

(4) a compound wherein Ra is H, Rb is cyclopropyl, E is a single bond and R is a *p*-(trifluoromethyl)phenyl, and

(5) a compound wherein Ra is a methyl, Rb is a 2-hydroxypropyl, E is a single bond and R is a 3-pyridyl).

3. (withdrawn) The pharmaceutical composition described in claim 2, wherein the first component is a nitrogen-containing heterocyclic compound selected from 6-Azocan-1-yl-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azepan-1-yl-3-(6-bromopyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 3-(3-methoxyphenyl)-6-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine, 3-(3-bromophenyl)-6-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azepan-1-yl-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(4-fluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(3-azabicyclo[3.2.1]octan-3-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(4,4-difluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(3,3-difluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azocan-1-yl-3-(6-bromopyridin-2-yl)-

1,2,4-triazolo[4,3-b]pyridazine, and 6-(8-azabicyclo[3.2.1]octan-8-yl)-3-(6-bromopyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, or a salt thereof.

4. (withdrawn) The pharmaceutical composition described in claim 2, wherein the second component is a bisphosphonate selected from alendronate, risedronate, pamidronate, incadronate, minodronate, ibandronate and zoledronate.

5. (withdrawn) The pharmaceutical composition described in any one of claims 1 to 4, wherein the bone mass increasing inducer is a preventive or therapeutic agent for a metabolic bone disease.

6. (withdrawn) The pharmaceutical composition described in any one of claims 1 to 4, wherein the bone mass increasing inducer is a preventive or therapeutic agent for a bone metabolism turnover reducing type (type II) osteoporosis.

7. (withdrawn) A combination product which is a bone mass increasing inducer consisting of two pharmaceutical preparations of a pharmaceutical preparation containing a non-living body-derived non-peptide osteoblast differentiation promoting compound as the first pharmaceutical preparation and a bisphosphonate as the second pharmaceutical preparation,

wherein said first and second pharmaceutical preparations are administered simultaneously or separately.

8. (withdrawn) The combination product described in claim 7, wherein the first pharmaceutical preparation is a pharmaceutical preparation comprising a nitrogen-containing heterocyclic compound represented by the general formula (I) of claim 2, or a salt thereof.

9. (withdrawn) The combination product described in claim 7 or 8, which is a kit comprising at least two pharmaceutical preparations of a pharmaceutical preparation containing a non-living body-derived non-peptide osteoblast differentiation promoting compound as the first pharmaceutical preparation and a bisphosphonate as the second pharmaceutical preparation.

10. (withdrawn) An agent for reinforcing the bone mass increasing effect of a non-living body-derived non-peptide osteoblast differentiation promoting compound, which comprises a bisphosphonate as the active ingredient.

11. (withdrawn) The agent described in claim 10, which is an agent for reinforcing the bone mass increasing effect of a nitrogen-containing heterocyclic compound represented by the general formula (I) of claim 2, or a salt thereof.

12. (withdrawn) An agent for reinforcing the bone mass increasing effect of a bisphosphonate, which comprises a non-living body-derived non-peptide osteoblast differentiation promoting compound as the active ingredient.

13. (withdrawn) The agent described in claim 12, which is an agent for reinforcing the bone mass increasing effect of a bisphosphonate, wherein it uses a nitrogen-containing heterocyclic compound represented by the general formula (I) of claim 2, or a salt thereof, as the active ingredient.

14. (withdrawn) Use of a non-living body-derived non-peptide osteoblast differentiation promoting compound and a bisphosphonate for producing a drug which is a bone mass increasing inducer.

15. (withdrawn) Use of a non-living body-derived non-peptide osteoblast differentiation promoting compound for producing a drug which induces increase of bone mass by the concomitant use of a bisphosphonate.

16. (withdrawn) Use of a bisphosphonate for producing a drug which reinforces bone mass increasing effect of a non-living body-derived non-peptide osteoblast differentiation promoting compound.

17. (Currently amended) A method for preventing or treating a metabolic bone disease which accompanies reduction of the bone mass and/or bone strength which comprises administering to a patient an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately.

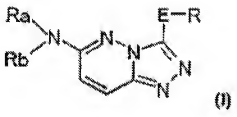
18. (Currently amended) The method according to claim 17, wherein the metabolic bone disease which accompanies reduction of the bone mass and/or bone strength is a bone metabolism turnover reducing type (type II) osteoporosis.

19. (withdrawn) A method for inducing bone mass gain of a patient, which comprises administering an effective amount of a non-living body-derived non-peptide osteoblast differentiation promoting compound and an effective amount of a bisphosphonate, simultaneously or separately, to a patient who requires increase of the bone mass and/or bone strength.

20. (withdrawn) The method described in any one of claims 17 to 19, wherein the non-living body-derived non-peptide osteoblast differentiation promoting compound is a

nitrogen-containing heterocyclic compound represented by the general formula (I) of claim 2, or a salt thereof.

21. (new) The method according to claim 17, wherein the non-living body-derived non-peptide osteoblast differentiation promoting compound is represented by the following general formula (I) or a salt thereof

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Ra and Rb: the same or different and each represent H; CO-lower alkyl; $SO_2$-lower alkyl; an optionally substituted cycloalkyl; an optionally substituted aryl; or a lower alkyl which may have 1 to 3 substituents selected from the group consisting of an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted 4- to 8-membered monocyclic saturated or partially unsaturated heterocyclic ring, CO-lower alkyl, $SO_2$-lower alkyl, $OR^1$, $SR^1$, $NR^1R^2$, a halogen, $NO_2$, CN and $COOR^1$; provided that at least one of Ra and Rb represents a group other than H; or,

Ra and Rb taken together with an adjacent N atom form a 4- to 8-membered saturated or partially unsaturated heterocyclic ring containing 1 or 2 N atoms as heteroatoms, said

heterocyclic ring may be fused with a benzene ring or a cycloalkyl ring and may have a bridge and may form a spiro ring, and said heterocyclic ring may have from 1 to 5 substituent groups,

E: a single bond, a $C_{1-3}$ alkylene, vinylene (-C=C-), ethynylene (-C≡C-), CO, $NR^3$, $CH_2$-J, $CONR^4$ or $NR^5CO$,

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R: an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl or an optionally substituted 4- to 8-membered monocyclic saturated or partially saturated heterocyclic ring,

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with the proviso that the following compounds are excluded:

(1) a compound wherein Ra and Rb taken together with an adjacent N atom form a piperidino, E is a single bond and R is a piperidino, unsubstituted phenyl, *p*-(trifluoromethyl)phenyl, *p*-chlorophenyl or *o*-nitrophenyl,

(2) a compound wherein Ra and Rb taken together with an adjacent N atom form a 4-methyl-1-piperazinyl, E is a single bond, and R is an unsubstituted phenyl, *p*-methylphenyl, *m*-methylphenyl, *p*-methoxyphenyl, *m*-chlorophenyl, *p*-chlorophenyl or *m*-nitrophenyl,

(3) a compound wherein R is an optionally substituted imidazolyl, 5-nitro-2-furyl or 5-nitro-2-thienyl,

(4) a compound wherein Ra is H, Rb is cyclopropyl, E is a single bond and R is a *p*-(trifluoromethyl)phenyl, and

(5) a compound wherein Ra is a methyl, Rb is a 2-hydroxypropyl, E is a single bond and R is a 3-pyridyl).

22. (new) The method according to claim 21, wherein the non-living body-derived non-peptide osteoblast differentiation promoting compound is a nitrogen-containing heterocyclic compound selected from the group consisting of 6-azocan-1-yl-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azepan-1-yl-3-(6-bromopyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 3-(3-methoxyphenyl)-6-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine, 3-(3-bromophenyl)-6-(piperidin-1-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azepan-1-yl-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(4-fluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(3-azabicyclo[3.2.1]octan-3-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(4,4-difluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-(3,3-difluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, 6-azocan-1-yl-3-(6-bromopyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, and 6-(8-azabicyclo[3.2.1]octan-8-yl)-3-(6-bromopyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine, or a salt thereof.

23. (new) The method according to claim 21, wherein the bisphosphonate is selected from the group consisting of alendronate, risedronate, pamidronate, incadronate, minodronate, ibandronate, and zoledronate.

24. (new) The method described in claim 17, wherein the non-living body-derived non-peptide osteoblast differentiation promoting compound is 6-(4-fluoropiperidin-1-yl)-3-(6-methoxypyridin-2-yl)-1,2,4-triazolo[4,3-b]pyridazine.